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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/039,718	01/03/2002	David S. Hungerford	21418-PA-DIV	4599

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EXAMINER	
NAFF, DAVID M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 10/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/039,718	HUNGERFORD ET AL.	
	Examiner	Art Unit	
	David M. Naff	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-83* is/are pending in the application.

4a) Of the above claim(s) *1-35,47-57 and 71-83* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36-46 and 58-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/13/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

In a response of 7/22/04 to a restriction requirement of 6/24/04, applicants elected Group IX claims 36-46 and 58-70 without traverse.

Claims 1-35, 47-57 and 71-83 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/22/04.

Claims examined on the merits are 36-46 and 58-70.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 36-46 and 58-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In line 4 of claim 36 and where recited in other claims, the specification fails to recite "spin-culture". While the specification discloses a "revolving culture chamber" (page 48, line 3 from the bottom) and a "spinning culture chamber" (page 55, last line), this is

not adequate support for the broader concept of "spin-culture" which can encompass culture in a chamber that does not spin where a stirrer in the chamber causes culture medium to rotate in a circular direction.

The specification fails to recite "progenitor mesenchymal cells" in line 3 of claim 61, as being cells to use in the invention, and adequate support for these cells in a Markush group as claimed is not found in the specification. While these cells are found in Table I, this table appears to describe cells known to be cultured on a microcarrier and not to describe cells used in the invention.

The specification fails to recite "collagen-coated biopolymers" in line 2 of claims 43 and 67. While collagen-coated dextran is disclosed (Table II), this does not support any biopolymer coated with collagen.

Claim Rejections - 35 USC § 112

Claims 36-46 and 58-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method as required by claims 36-46 wherein spin-culture is with revolving culturing chamber and the microcarrier is that of claim 43 or 44 (with the exception of collagen-coated biopolymer) and for the method of claims 58-70 when the cells are chondrocytes, spin-culture is with a revolving culture chamber and the microcarrier is that of claim 67 or 68 (with the exception of collagen-coated biopolymer), does not reasonably provide enablement for other embodiments within

the scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification describes only a revolving culture chamber for spin-culture required in the claims, and it would be speculation and unpredictable as to another form of spin-culture that will provide the desired results of the invention. Only a microcarrier set forth above has been demonstrated to provide the disclosed result of recovering a high yield of functional cells, and it would be speculation and unpredictable as to another microcarrier that will function as those actually used. The specification describes advantages of the invention only with respect to chondrocytes (pages 55-56). While other cells are disclosed that can be used, advantages of the invention are described only with respect to chondrocytes, and essentially all specific culturing on microcarriers involves the of chondrocytes. The claims must be commensurate in scope with the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-46 and 58-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out

and distinctly claim the subject matter which applicant regards as the invention.

In claims 36 and 58, "a different part of the patient's body" is confusing as the part the different part is different from.

In line 3 of claim 36 and where recited in other claims, "high-quality" is uncertain as to meaning and scope. Being "high" in quality is relative and subjective. It is suggested this term be deleted.

In line 4 of claim 36 and where recited in other claims, "spin-culture" is uncertain as to the culture method required. The specification fails to recite this term, and it is uncertain as to culture processes that are spin-culture and not spin-culture. It is suggested that "spin-culture" be replaced with --- revolving culture chamber --- as described in the specification.

In line 2 of claims 38 and 62, "orthopedic purposes" is uncertain as to "purposes" that are orthopedic and not orthopedic.

In line 1 of claims 38, 59 and 60, "conveniently" is uncertain as to meaning and scope since being convenient is relative and subjective. This term should be deleted.

In line 3 of claim 43, "or" should be replaced with --- and --- for a proper Markush group. To be consistent with claim 43, claim 67 should be amended to require a Markush group as claim 43 by in line 2 inserting --- the group consisting of --- after "from", and in line 3 changing "or" to --- and ---.

In claims 40 and 64 (line 2), a "reduced oxygen environment" is uncertain as to meaning and scope since being "reduced" is relative and subjective depending on the oxygen content compared with.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 36-39, 42-46, 58-63 and 66-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glorioso et al (6,413,511 B1) in view of Frondoza et al and Schinstine et al (5,858,747) and Cherksey (6,264,943 B1), and if necessary in further view of Armstrong (5,830,507).

The claims are drawn to a method of repairing diseased or injured tissue by surgically obtaining healthy tissue or a healthy chondrocyte specimen from a different part of a patient's body, rapidly growing cells from the tissue or chondrocytes externally of the patient's body

by spin-culture on microcarrier particles, and surgically implanting the grown cells or the grown chondrocytes into the diseased or injured tissue of the patient.

Glorioso et al disclose (col 6, lines 31-45 and col 28, lines 20-25) transplanting transfected chondrocytes to repair a defect such as an articular cartilage defect (col 15, lines 62-67). Autologous chondrocytes are retrieved for *in vitro* culture (col 45, lines 30-35) prior to transfection and transplantation (col 29, lines 5-12).

Frondoza et al disclose culturing of chondrocytes on microcarriers in a spinner flask (page 881, left col). Microcarriers used include dextran beads, collagen-coated dextran beads, crosslinked dextran containing N,N,N-trimethyl-2-hydroxyaminopropyl groups and crosslinked dextran containing covalently bound type I collagen (page 880, right col). Microcarrier suspension culture supported growth and enhanced expression of the chondrocytic phenotype (abstract, page 879).

Schinstine et al disclose (col 3, lines 17-45) that when cells do not have a substrate available in a bioartificial organ (BAO), the cells tend to adhere to each other and form dense agglomerations or aggregates that can develop necrotic regions due to relative inaccessibility of nutrients and oxygen. Microcarriers can provide a growth surface in the BAO (col 17, lines 24-54). The microcarriers can allow a greater number of cells to be encapsulated and evenly distributed within the BAO. The microcarrier can be a Cytodex dextran

microcarrier or be collagen or EMC coated microcarriers (col 17, lines 29-39).

Cherksey discloses (col 5, lines 9-18) that culturing cells *in vitro* on a support matrix such as glass beads before the cells are transplanted into a mammalian brain results in prolonged survival and viability *in vivo*.

Armstrong discloses (col 3, lines 46-54), in reference to the prior art, that it is known to attach hepatocytes to collagen-coated cross-linked dextran microcarriers, and implant the microcarriers in the peritoneal cavity of rats. The microcarriers provide a surface of attachment so the hepatocytes survive and function *in vivo*. The microcarriers do not degrade once implanted. Armstrong further discloses, in regard to the invention, culturing cells with microcarriers such as cross-linked dextran to provide cell-coated microcarriers, and using the cell-coated microcarriers to repair a skin injury (col 5, line 6 to col 7, line 7). The cell-coated microcarriers can be harvested, concentrated and put into maintenance medium for shipment to a remote treatment center (col 14, lines 41-52). Due to a uniform suspension of microcarriers, each microcarrier has a similar number of attached cells resulting in a homogeneous population for subsequent application on a skin injury (col 7, lines 35-42).

When culturing chondrocytes for implanting as disclosed by Glorioso et al, it would have been obvious to culture the chondrocytes on a microcarrier in a spinner flask as suggested by Frondoza et al

disclosing this method of culturing as supporting chondrocyte growth and enhancing phenotye, and as further suggested by Schinstine et al disclosing culturing cells on microcarriers to prevent the formation of necrotic regions and as also suggested by Cherksey disclosing that culturing cells on glass beads before transplanting into the mammalian brain results in prolonged survival and viability *in vivo*. Obtaining cells from a different part of the body would have been obvious to not further damage an injury being repaired and Glorbioso et al discloses using autologous cells. If needed, Armstrong would have further suggested the invention from a disclosure of culturing cells on microcarriers before implanting. The conditions of dependent claims would have obvious matters of choice depending on individual preference in view of conditions disclosed by the references. Selecting a specific region of the body to obtain the cells and to implant the cells would have been a matter of individual preference depending on the tissue defect to be repaired. In regard to claims directed to a crosslinked polysaccharide, Frondoza et al disclose crosslinked dextran containing covalently bound type I collagen, and a polysaccharide crosslinked with a polyamine such as dextran crosslinked with gelatin would have been obvious therefrom.

Claim Rejections - 35 USC § 103

Claims 40, 41, 64 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over the references as applied to claims 36-39, 42-46, 58-63 and 66-70 above, and further in view of Starling et al (4,839,215).

The claims require culturing the cells in a reduced or low oxygen environment.

Starling et al disclose culturing chondrocytes (col 18, line 62) in a carbon dioxide incubator (col 19, lines 1-5). The cells maintained their phenotype and increased in number over hundred fold.

When culturing the chondroctyes of Glorioso et al on a microcarrier and in a spinner flask as set forth above, it would have been obvious to culture in a carbon dioxide atmosphere as suggested by Starling et al disclosing culturing chondrocytes in a carbon dioxide incubator where phenotype is maintained and the number of cells is increased over a hundred fold. Maintaining phenotype and increasing cell number over a hundred would have been expected to be an advantage. The carbon dioxide atmosphere would have provided a reduced oxygen content as claimed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 36-39, 42-46, 58-63 and 66-70 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,378,427 B1 or claims 1-9 of U.S. Patent No. 6,662,805 B2 in view of Frondoza et al.

The claimed invention and Frondoza et al are described above.

The claims of the patents require a method substantially as presently claimed except for culturing the chondrocytes on a microcarrier using spin-culture.

It would have been obvious to culture the chondrocytes of the claims of the patents with a microcarrier using a spinning flask as disclosed by Frondoza et al when culturing chondrocytes since this culturing method is suggested by Frondoza et al as an advantageous method for culturing chondrocytes.

It does not appear the present claims are non-elected claims resulting from a restriction requirement as compared to the claims of the patents.

Double Patenting

Claims 40, 41, 64 and 65 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 6,378,427 B1 or claims 1-9 of U.S. Patent No. 6,662,805 B2 in view of Frondoza et al as set for above, and in further view of Starling et al.

The invention and Starling et al are described above.

When using a microcarrier and spinning flask in the methods of the claims of the patents claims as set forth above, it would have

been obvious to culture in a carbon dioxide atmosphere as suggested by Starling et al disclosing culturing chondrocytes in a carbon dioxide incubator where phenotype is maintained and the number of cells is increased over a hundred fold. Maintaining phenotype and increasing cell number over a hundred would have been expected to be an advantage. The carbon dioxide atmosphere would have maintained a reduced oxygen content as claimed.

Double Patenting

Claims 36-46 and 58-70 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23 of copending Application No. 10/654,057 or claims 1-35 of copending Application No. 10/066,992. Although the conflicting claims are not identical, they are not patentably distinct from each other because the presently claimed invention of using spin-culture to culture cells on microcarriers to repair defective tissue would have been obvious from the claims of the copending applications that contain claims requiring culturing chondrocytes on microcarriers using spin-culture conditions and a low oxygen environment to produce chondrocytes for implanting.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Double Patenting

Claims 36-39, 42-46, 58-63 and 66-70 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-51 of copending

Application No. 09/825,632. Although the conflicting claims are not identical, they are not patentably distinct from each other because the presently claimed invention would have been obvious from claims of the copending application including claims drawn to culturing chondrocytes on a microcarrier for implanting and claims that require a spinner culture apparatus for culturing.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Double Patenting

Claims 40, 41, 64 and 65 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-51 of copending Application No. 09/825,632 as set forth above, and further in view of Starling et al who would have suggested a low oxygen environment when culturing for reasons set forth above when applying Starling et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is 571-272-0920. The examiner can normally be reached on Monday-Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David M. Naff
Primary Examiner
Art Unit 1651

DMN
10/28/04